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Fragment-Based Drug Discovery of SARS-CoV-2 Therapeutics

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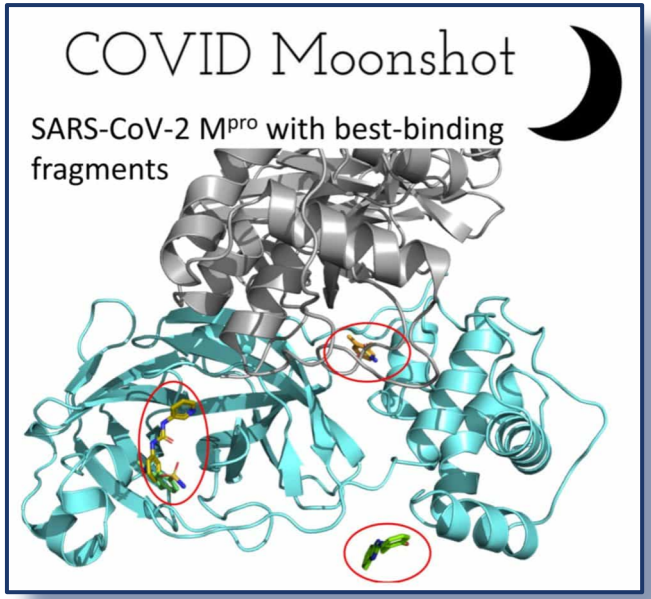
Introduction

- The novel SARS-CoV-2 was first identified in late 2019.
- COVID Moonshot is an international consortium of drug designers.
- Moonshot's X-ray crystallography of the Main Protease (Mpro) provided a starting fragment.
- Targeting the Mpro would be the most effective approach to inhibiting the replication of the virus.



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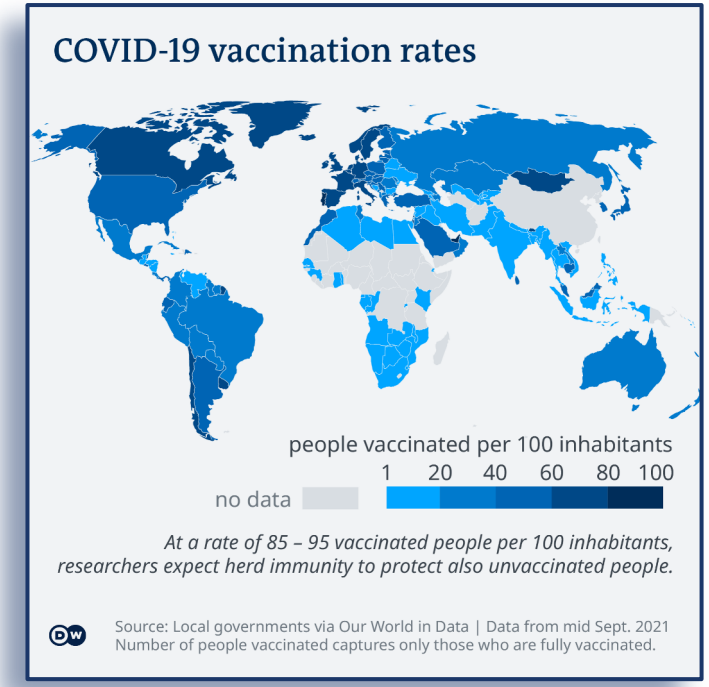
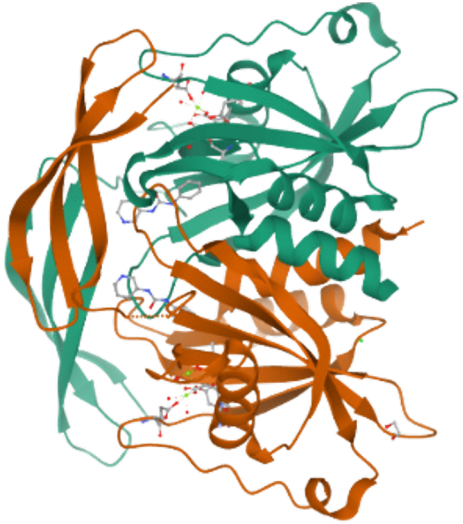


The Need for an Oral Antiviral

- While vaccines prevent contraction of the virus, oral antiviral medications inhibit the replication of the virus after contraction.
- Antiviral medications are complementary to vaccines and public health restrictions.
- Vaccines are not 100% effective, especially against new strains of the virus.
- Oral antivirals are easier to make and distribute.

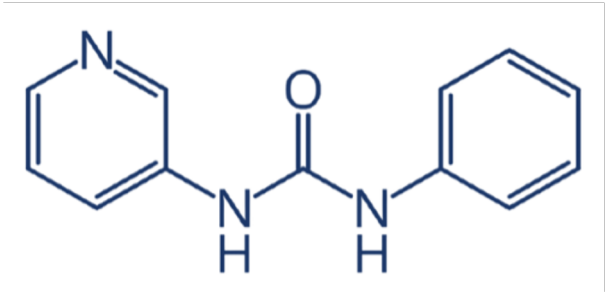
Methodology: SeeSAR

Fragment x0434 was selected from the Moonshot database of fragments that had not yet been analyzed by anyone in the project. The respective Protein Data Bank (PDB) code (5QJ5) was entered into SeeSAR.



Left: fragment x0434

Right: protein code 5QJ5



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Methodology: SeeSAR

- The fragment was used to design new structures using SeeSAR.
- The *Binding Site* mode showed all residues within a 6.5 Angstrom radius. All residues were added around the binding site.
- In the *Inspirator* mode, 502 poses for the binding site with desirable binding affinities were generated.
- Molecules were sorted for further analysis.

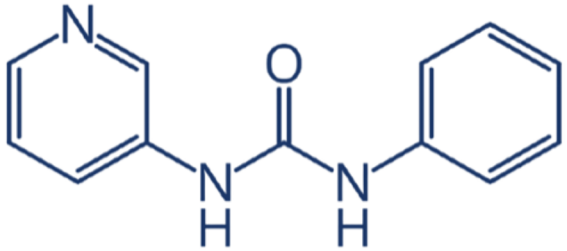
Methodology: SwissADME

- Fragments were entered into SwissADME program.
- Six main properties were investigated:
  - Lipinski's rule (0 violations)
  - GI absorption (High)
  - Leadlikeness (0 violations)
  - PAINS (0 alert)
  - 5 CYP inhibitors (No)
  - BBB permeability (Yes)

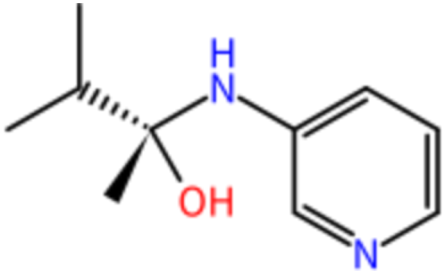
SwissADME Results: Most Promising Molecules

Molecule	Lipinski's Rule	GI Absorption	Leadlikeness	PAINS	CYP Inhibition	BBB Permeability	Average Estimated Binding Affinity (nM)
1	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	180869
2	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N Y N	Y	321065
3	Yes; 0 violation	High	Yes	0 alert	N N N Y N	Y	476753
4	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	Y N N N N	Y	493266
5	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	705047
6	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	705836
7	Yes; 0 violation	High	Yes	0 alert	N N N N N	Y	899362
8	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	Y N N N N	Y	1134899
9	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	1539655
10	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	1707485
11	Yes; 0 violation	High	No; 1 violation: MW<250	0 alert	N N N N N	Y	3870240

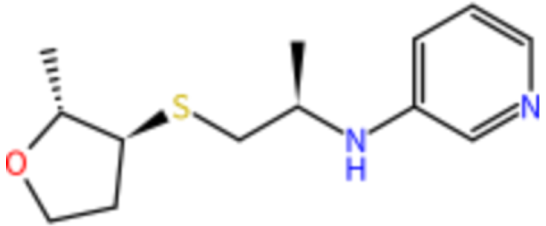
Top Three Molecular Structures



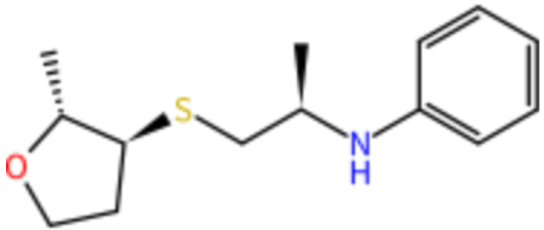
beginning fragment x0434



molecule 1



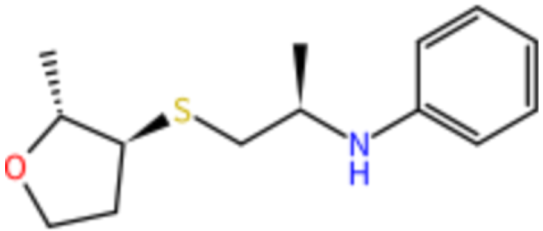
molecule 2



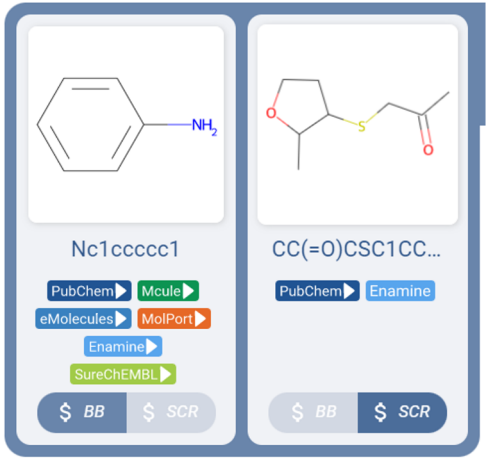
molecule 3

Molecule 3

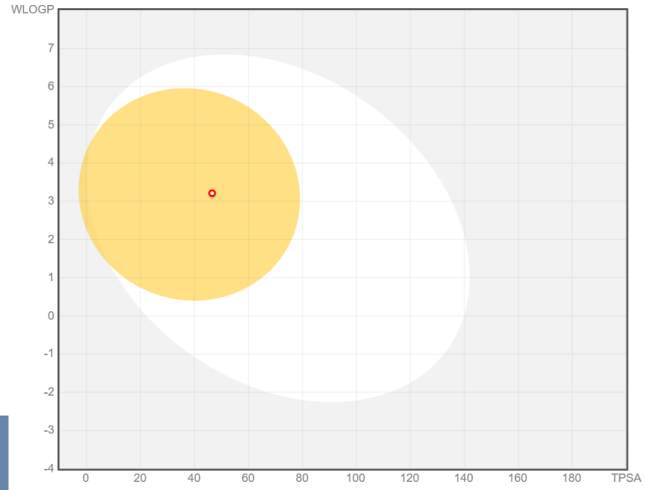
- no Leadlikeness violations
- *drawback:* 1 CYP inhibitor
- *average binding affinity:* 476753 nM
- one-step synthesis route



molecule



a possible synthesis route



BOILED-egg diagram

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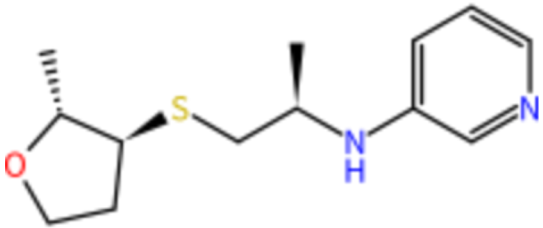
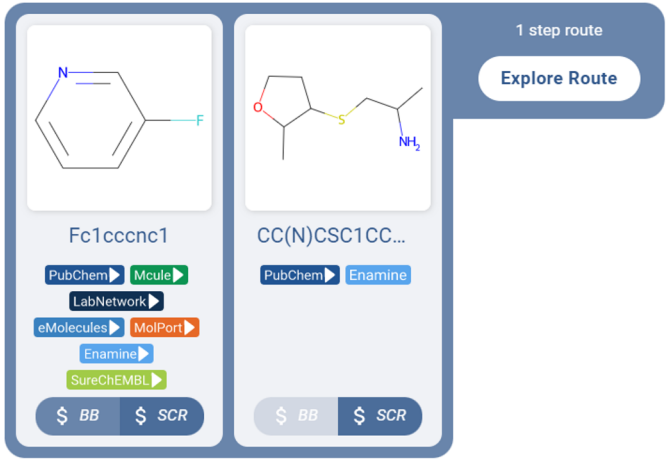
Molecule 2

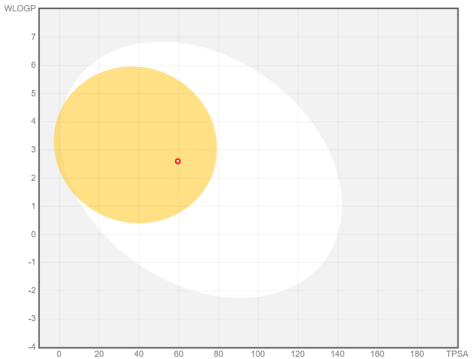
- *drawbacks:* 1 Leadlikeness violation: Mw<250, 1 CYP inhibitor
- *average binding affinity:* 321065 nM
- one-step synthesis route



molecule 2



a possible synthesis route



BOILED-egg diagram

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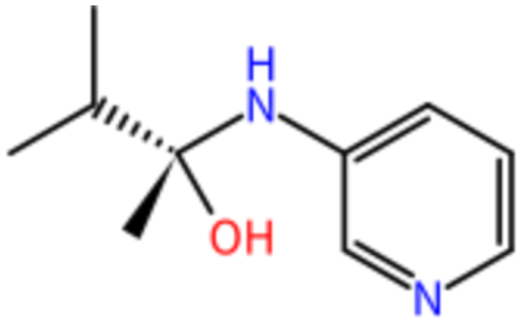
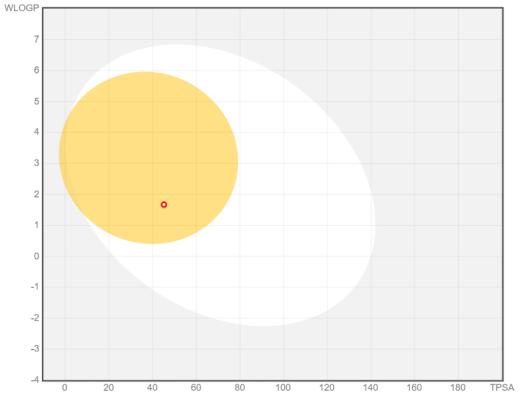
Molecule 1

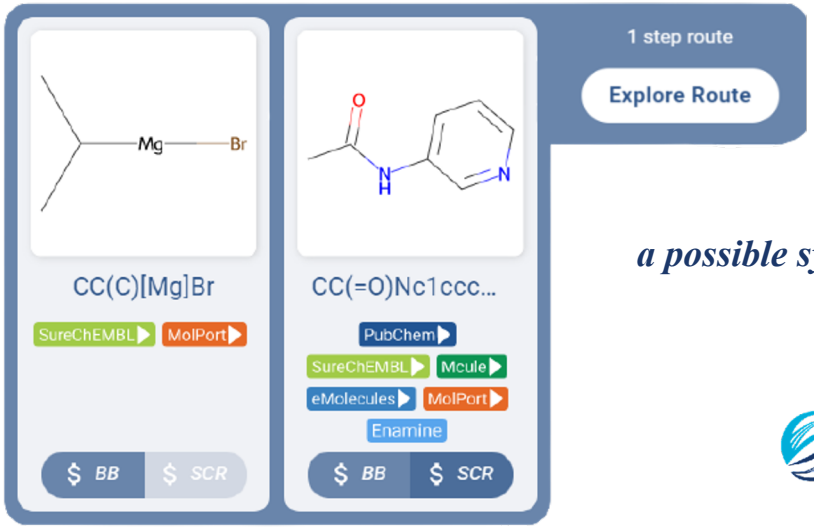
- no CYP inhibition
- *drawback:* 1 Leadlikeness violation: Mw<250
- *average binding affinity:* 180869 nM
- one-step synthesis route



molecule 1



BOILED-egg diagram



a possible synthesis route

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Conclusion

- A fragment was selected from the COVID Moonshot Database, and then it was processed in SeeSAR.
- SwissADME was used to look at various drug-like properties to determine which molecules would be most suitable as an oral antiviral.
- The top molecules were identified. They will move on to synthesis and further collaboration with the COVID Moonshot initiative.

Special thanks to...

Dr. John Thurmond

Student Inquiry and Research

Illinois Mathematics and Science Academy

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